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IGF2BP1 IS A POOR PROGNOSTIC FACTOR IN EXTRAHEPATIC CHOLANGIOCARCINOMA

Oncology

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ABSTRACT

Introduction: IGF2BP1 has been shown to play an important role in cell proliferation and growth of normal tissues and tumor tissues, as well as tumor cell adhesion, apoptosis, migration, and invasion. Therefore, IGF2BP1 is considered one of the most promising therapeutic targets in cancer treatment. In the current study, we try to see the role of IGF2BP1 in extrahepatic cholangiocarcinoma.

Methods: We retrospectively and randomly selected patients who treated extrahepatic cholangiocarcinoma between 2003 and 2004. Tissue microarray was constructed and immunohistochemical stain of IGF2BP1 and variaous tumorigenesis markers were stained.

Results: Samples from thirteen patients with extrahepatic cholangiocarcinoma were included in the current study. The mean ages at diagnosis were 64.8 years and 46.2% of patients was female. According to the Kaplan-Meier survival plot, the high-IGF2BP1 expression group showed poor overall survival with p value of 0.007.

Conclusion: we found IGF2BP1 was a poor prognostic factor in extrahepatic cholangiocarcinoma. Further large-scale studies are needed for exploration.

KEYWORDS

Cholangiocarcinoma, IGF2BP1, prognosis, immunohistochemical

INTRODUCTION

Biliary tract cancer is a group of malignant tumors that develop in the bile ducts and gallbladder. Biliary tract cancer includes intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer [1] Biliary tract cancer is particularly high prevalence in countries such as Korea, Thailand, China and Chile. It is rare in most western countries. However, the incidence of this disease is increasing worldwide. [2] Biliary tract cancer is known to have a poor prognosis, with an overall 5-year survival rate of about 6-26% for local diseases and 1-2% for metastatic diseases. [3] However, the median overall survival of patients with inoperable or metastatic biliary tract cancer treated with chemotherapy was still miserable. Local biliary tract cancer indicates no response with effective adjuvant therapy and neo-adjuvant therapy. A retrospective analysis of 156 extrahepatic cholangiocarcinoma and gallbladder cancer resections found that the pattern of recurrence was different depending on the primary site. Local recurrence was more common in extrahepatic cholangiocarcinoma (65%) compared with gallbladder cancer (28%), while distant metastasis is dominant in gallbladder cancer (72%) compared with extrahepatic cholangiocarcinoma (36%) as an initial recurrence site [6]. Therefore, a multidisciplinary approach with shared decision-making is essential for the successful management of resectable biliary tract carcinoma. Due to the difference of the primary site of biliary tract carcinoma, we choose extrahepatic cholangiocarcinoma as the study target in the current study.

Insulin-like protein binding protein-2 mRNA 1 (IGF2BP1), a member of the group of conserved single-chain RNA binding proteins (IGF2BP1-3), is more diverse and expresses in a broad range of fetal tissues and more than 16 cancers but only in a limited number of normal adult tissues. This gene is required for the transport of certain mRNAs, which play an important role in embryonic formation, carcinogenesis, and resistance to chemotherapy [7, 8]. The IGF2BP1 is a crucial regulator of tumor and stem cell fate and its elevated expression in a multitude of tumors is associated with poor prognosis [9, 10]. Previous studies have shown that IGF2BP1 promotes mRNA stability in many tumors, various types of solid cancer and stem cells [11-13]. The general principle of this regulation is the control of mRNA turnover by impairing microRNA-dependent downregulation of target mRNAs encoding pro-oncogenic factors [14].

Numerous in vivo and in vitro studies have found cancer-related mRNAs such as PTEN, ACTB, MAPK4, MKI67, c-MYC, and CD44, and by regulating these mRNAs, IGF2BP1 has been shown to play an important role in cell proliferation and growth of normal tissues and tumor tissues, as well as tumor cell adhesion, apoptosis, migration, and invasion [11]. Therefore, IGF2BP1 is considered one of the most promising therapeutic targets in cancer treatment. In the current study, we try to shed light on the role of IGF2BP1 in extrahepatic cholangiocarcinoma.

METHODS

Patients

We retrospectively and randomly selected patients who treated extrahepatic cholangiocarcinoma at Cardinal Tien Hospital between 2003 and 2004. None of these patients had a family history of hereditary cancer or malignancy in a first-degree relative, according to interviews completed at the time of admission for surgery. All the patients with malignant disease had undergone routine Whipple operation or tumor resection with concurrent regional lymphadenectomy. We excluded patients who had received chemotherapy or radiation therapy before resection. Finally, 13 patients were included in this study. All patient clinical charts and histopathology reports were reviewed for data regarding age, gender, tumor size, surgical margin status, lymph node metastasis or distant metastasis and TMN staging. All patients were followed for 1 to 10 years. The median follow-up period was 3.2 years. All enrolled patients were de-linked anonymously for protection, and this study protocol was approved by the Institutional Review Board of Cardinal Tien Hospital.

Tissue Microarray Construction

All tissue samples were routinely fixed in formalin and embedded in paraffin wax. Then, all the tissue samples were determined via standard hematoxylin and eosin (H&E) staining, obtained paraffin blocks of these samples using a 2.0-mm punch, and inserted the samples into recipient paraffin blocks to form complete tissue arrays. Sections of 4 μm were cut from these complete array blocks and transferred to salinized glass slides.

Histology, Immunohistochemistry And Scoring

The abovementioned paraffin-embedded tissue array blocks were cut into 5-μm-thick sections for H&E staining. For each sample, the carcinoma type, degree of cell differentiation, growth pattern, tumor cell nuclear morphology, degree of metaplasia, degree of calcification, extent of necrosis, mitosis count and other specific indices of differentiation were re-checked by a pathologist. Immunohistochemicl stain (IHC) staining was performed using a Ventana BenchMark XT automated stainer (Ventana, Tucson, AZ, USA) and primary antibodies for IGF2BP1 (1:75, rabbit, catalog number: ab82968, Abcam, MA, US), Ki-67 (1:100, mouse, catalog number: 350503, BioLegend, CA, US), Caspase-3-cleaved (1:100, Rabbit, catalog number: 9664, Cell Signaling, MA, US), CD31 (1:500, rabbit, catalog number: 250590, Abbiotec, CA, US), E-cadherin (1:100, rabbit, catalog number: ab40772, Abcam, MA, US), N-cadherin (1:75, rabbit, catalog number: ab76011, Abcam, MA, US), Fibronectin (1:50, Mouse, catalog number: SC-8422, Santa cruz, TX, US), AKT-phophorylated (1:50, mouse, catalog number: GTX11901, GeneTex, CA, US), ERK-phophorylated (1:200, rabbit, catalog number: Af1018 R&D, MN, US), STAT3-phophorylated (1:50, rabbit, catalog number: ab76315, Abcam, MA, US), and AMPK-

phophorylated (1:100, rabbit, catalog number: 2535, Cell signal). Experienced pathologist (HC Maa) reviewed the IHC slides, and immunostaining intensity was recorded as 0 for no staining, 1 for faint staining, 2 for moderate staining, and 3 for intense staining. The staining percentage of each core, ranging from 0% to 100%, was also recorded. Then, an H-score ranging from 0 to 300 was calculated by multiplying the staining intensity by the percentage of each core.

Statistical Analyses

All statistical analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL). To test for differences between positive and negative IHC expression, chi-square analysis was performed for categorical variables. To test for differences H-score, a t-test was used. Simple bivariant correlation was applied for the correlation between 2 markers' H-score. Finally, **Kaplan-Meier** survival curves were generated, and overall survival was calculated using the log-rank test. All statistical tests were two-sided, and the results were considered statistically significant when $p < 0.05$.

RESULTS

Samples from thirteen patients with extrahepatic cholangiocarcinoma were included in the current study. The mean ages at diagnosis were 64.8 years and 46.2% of patients was female (Table 1). Moderate differentiation, T3 /T4, presence of lymph node metastasis and incomplete surgical margin were not statistically significant in the expression of IGF2BP1. When correlated with tumorigenesis markers of proliferation (Ki-67), apoptosis (Caspase 3), angiogenesis (CD31), EMT markers (E-cadherin, N-cadherin, fibronectin), and tyrosine kinase of Akt, Erk, STAT3 and AMPK, all were non-significant. This may be due to the small sample size in the current study (Table 2). The expression level of IGF2BP1 showed more in female than male and incomplete surgical margin than complete surgical margin. However, no significance was reached (Figure 1). According to the Kaplan-Meier survival plot (Figure 2), the high-IGF2BP1 expression group showed poor overall survival with p value of 0.007.

Table 1 Demographic Data Of The Study Subjects

		IGF2BP1			
		Low expression		High expression	
Age (years)	65	1	(16.7%)	5	(83.3%)
	65	2	(28.6%)	5	(71.4%)
Gender	Male	2	(28.6%)	5	(71.4%)
	Female	1	(16.7%)	5	(83.3%)
Differentiation	Well	0	(0.0%)	2	(100.0%)
	Moderate	3	(27.3%)	8	(72.7%)
T stage	T1 / T2	1	(12.5%)	7	(87.5%)
	T3 / T4	2	(40.0%)	3	(60.0%)
Lymph node metastasis	Absence	1	(12.5%)	7	(87.5%)
	Presence	2	(40.0%)	3	(60.0%)
Complete surgical margin	Yes	2	(20.0%)	8	(80.0%)
	No	1	(33.3%)	2	(66.7%)

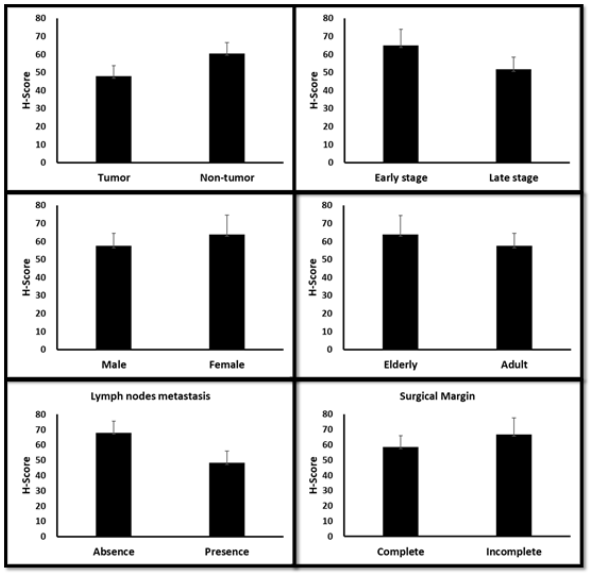

Figure 1 H-score Difference Of IGF2BP1 In Various Groups

Table 2 Correlation Of IGF2BP1 And Tumorigenesis Markers

Markers		r	p
Proliferation	Ki67	0.201	0.510
Apoptosis	Caspase 3	-0.411	0.163
Angiogenesis	CD31	-0.238	0.434
EMT	E-cadherin	0.450	0.123
	N-cadherin	0.050	0.870
	Fibronectin	-0.380	0.200
Kinase	pAkt	0.144	0.639
	pErk	-0.113	0.713
	pStat3	-0.112	0.716
	pAMPK	-0.156	0.612

EMT: epithelial mesenchymal trsistion

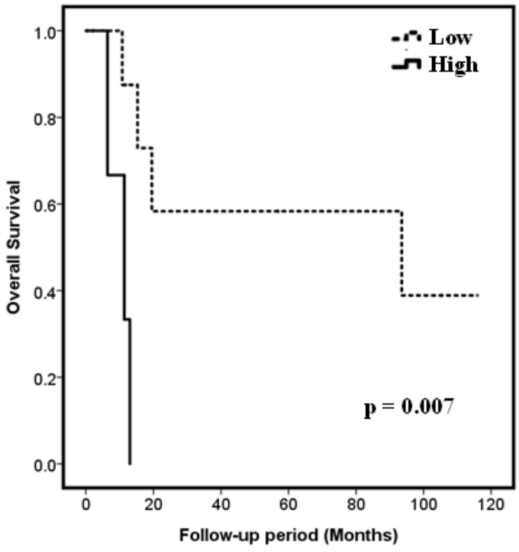

Figure 2 Overall Survival Of The IGF2BP1

DISCUSSION

Expression members of the IGF2BP family has been linked to several cancers. However, most reports only consider IGF2BP1 and IGF2BP3. IGF2BP is primarily cytoplasmic and often granular appearance. A nuclear role of IGF2BPs remains controversial, However, there is now evidence that IGF2BP can bind to the target mRNA at the transcription site [15, 16]. Consistently, IGF2BP is found in the nucleus of spermatogenic cells, indicating the presence of a nuclear export signal in it [17]. In the cytoplasm, IGF2BP produces isolated ribonucleic protein (RNP) granules and is enriched in the peri-nuclear region. It is also found in neurites of developing neurons that support the role of IGF2BP in promoting mRNA translation [18, 19].

Most studies have serious differences between pure functional invitro studies and more descriptive clinical oncology/epidemiological studies. For example, there is a number of in vitro evidences of IGF2BP1 regarding the promotion of cellular motility, but the importance of IGF2BP1 in the process of cancer metastasis is not really confirmed by in vivo studies. Likewise, we still have little information on a putative co-regulation of IGF2BP1 and target mRNA expression in primary tumor samples, although the expression of IGF2BP1 has, for instance, been correlated with lymph node metastasis of colorectal carcinomas [20].

Studies in other cancer models have confirmed the role of IGF2BP1 in promoting additional cancer hallmark pathways, including MYC/MYCN driven gene expression demonstrated in ovarian cancer [21] liver cancer [22,23], neuroblastoma [24] and KRAS-driven signaling in lung adenocarcinoma [25]. In gallbladder cancer, IGF2BP 2 immunoreactivity was seen in 74.3% of tumor samples in tissue microarray samples, of which 14.0% showed strong staining intensity, and 86.0% showed low staining intensity. 72.4% of tumor samples were positive for IGF2BP1, but IGF2BP1 had lower expression in tumor tissues compared to other tissues. Kaplan Meier assay has been linked to shorter survival times with higher IGF2BP2 expression ($p = 0.033$), IGF2BP1 expression was associated with a shorter survival time. IGF2BP2 is frequently overexpressed in gallbladder cancer and is significantly associated with prognosis and growth rate in in vivo.

[26]. In our study, we found IGF2BP1 also serve as a poor prognostic factor in extrahepatic cholangiocarcinoma.

Moreover, overexpression of miR-885-5p directly inhibited GALNT3 and also indirectly promoted IGF2BP1 downregulation, inhibiting metastasis and proliferation of intrahepatic cholangiocarcinoma. In addition, miR-885-5p inhibited metastasis of intrahepatic cholangiocarcinoma by down-regulating the signaling pathway of PI3K/AKT/MMP [27]. IGF2BP1 was highly expressed in lung cancer cells treated with high glucose. IGF2BP1 knockdown inhibited the proliferation, migration, and invasion of lung cancer cells, and induced cell cycle arrest and apoptosis [28]. In addition, in breast cancer, the hypoxic-induced long-chain non-coding RNA KB-1980E6.3 recruited IGF2BP1 to retain the stability of c-Myc mRNA [29]. Other studies have shown that the expression of IGF2BP1 is increased in endometrial cancer and that high expression of this protein correlates with poor prognosis. Overexpression of IGF2BP1 may promote cell proliferation and regulate tumor cell cycle and cancer progression [30].

In conclusion, we found IGF2BP1 was a poor prognostic factor in extrahepatic cholangiocarcinoma. However, no specific correlation was seen in the apoptosis, proliferation, angiogenesis, or epithelial mesenchymal transition in extrahepatic cholangiocarcinoma. This may be due to the small sample size in the current study. Further large-scale studies are needed for exploration.

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